DATA AND SAFETY MONITORING PLAN (DSMP)

Template and Guidelines

January 2017

PREFACE

Investigators should consider using this template when developing the Data and Safety Monitoring Plan (DSMP) for clinical studies supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

The goal of the DSMP is to provide a general description of a plan that you intend to implement for data and safety monitoring. The DSMP should specify the following:

- *Potential risks for participating in the study*
- *Procedures for data review and reporting for adverse events*
- *The entity responsible for monitoring the study (referred to as "Monitoring Body"). These can include, but are not limited to, monitoring by a:*
  - *Project Director (PD)/Principal Investigator (PI) (required)*
  - *Institutional Review Board (IRB) (required)*
  - *Designated medical monitor*
  - *Internal Committee or Board*
  - *Independent, NIAMS-appointed Monitoring Body (MB) which can include a Data and Safety Monitoring Board (DSMB), an Observational Study Monitoring Board (OSMB), or a Safety Officer (SO).*
- *Content and format of the safety report*
- *Responsibilities of study staff and monitoring entity*

Note that all instructions and explanatory text are shown in italics and should be replaced with the study specific text. There is no need to include sections that are not relevant to the particular study.

TABLE OF CONTENTS

1.0 PARTICIPANTS SAFETY

1.1 Potential Risks and Benefits for Participants

This section outlines the potential risks and benefits of the research for the study participants and for society. It should include a description of all expected adverse events (AEs), the known side effects of the intervention, and all known risks or complications of the outcomes being assessed.

Potential Risks: (*Outline potential risks for study participants*.)

Example: The potential risks to study participants include *(e.g., there may be temporary slight discoloration of the skin after blood draws.)*

Potential Benefits: (*Outline potential benefits for study participants or if there are no direct benefits to the participants*.)

Example: The potential benefits to study participants include *(e.g., ongoing nutritional counseling will be provided to all participants).*

1.2 Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UPs)

This section should describe how to identify AEs SAEs and UPs. In the case where the intervention is a Food and Drug Administration (FDA) regulated drug, device or biologic, it should include the FDA definition, grading scale and "study relatedness" criteria of AEs. It should also include the Office for Human Research Protections (OHRP) reporting requirements.

This section should also describe who is responsible for reporting these events and the roles and responsibilities of each person on the clinical study team who is involved in the safety reporting. The timeline for reporting SAE and targeted non-serious AE to the entity conducting the monitoring, the IRBs, the NIAMS through their Executive Secretary and, if appropriate, the FDA should be specified.

1.3 Protection against Study Risks

This section provides information on how risks to participants will be managed. It should specify any events that would preclude a participant from continuing in the study. This section should also include the informed consent process. In general, the format and content of this section are similar to the Human Subjects section of the grant application.

Informed Consent Process. *Explain the informed consent process.*

Example: The consent process informs a volunteer about the study, indicates the participation is voluntary and he/she has the right to stop at any time. Risks are

enumerated in the informed consent form and described orally during the consent process.

Protection against Risks. *Describe measures to protect participants against study specific risks.*

Example: The procedures to protect against risks *(describe known risks)* include *(e.g., a safe, hygienic environment for all medical procedures and an experienced, certified staff)*

2.0 INTERIM ANALYSIS & STOPPING RULES

This section provides information on planned interim analysis. Interim analysis may be conducted either due to pre-specified stopping rules as outlined in the protocol and at predetermined intervals, or as determined necessary by the monitoring entity to assess safety concerns or study futility based upon accumulating data. An interim analysis may be performed for safety, efficacy and/or futility, and the reports are prepared by the unmasked study statistician or data coordinating center responsible for generating such reports. Rules for stopping the study, based on interim analysis, should be described.

Example: Interim analysis of the study is planned according to the alpha spending rule [Lan and DeMets, 1994]. The proportion of expected events is considered as the information statistic. The p-values are constructed to maintain the overall study power of 0.05, two-sided. If the test statistic exceeds the boundary, then the study could be considered for early termination due to emerging differences. The interim look is recommended at the end of year one as we expect approximately 50% of the patients followed for at least six months.

3.0 DATA AND SAFETY MONITORING

This section identifies the name of the individual or entity responsible for data and safety monitoring what information will be reviewed and frequency of such reviews.

Procedures should be described for the following:

- *Frequency of reports and reporting to the IRB, the monitoring entity and NIAMS through their Executive Secretary and, if appropriate, the FDA.*
- *Routine review of AEs and UPs by the IRB, the monitoring entity, NIAMS, etc.*
- *Specific triggers for ad hoc review (e.g., deaths, threshold for SAE) as well as the process for ad hoc review.*

Example: The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to his or her Institutional Review Board (IRB), and the NIAMS and the monitoring body (through the Executive Secretary), and FDA as required. The study statistician prepares reports that list adverse events, serious adverse events, deaths,

and disease-or treatment-specific events required for monitoring body review in order to ensure good clinical care and identify any emerging trends. The Monitoring Body (MB) will act in an advisory capacity to the NIAMS to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

3.1 Frequency of Data and Safety Monitoring

This section describes the frequency of data and safety monitoring reviews.

Example: The PI will be informed of serious adverse events as soon as they occur by the study coordinator and will notify the NIAMS and Monitoring Body (MB) *w*ithin 48 hours of becoming aware of the event. The PI will report the Serious Adverse Events and Unanticipated Problems to his or her IRB within 5 business days of becoming aware of the event, according to local IRB requirement. Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if there are unforeseen deaths or the threshold for SAE has been met.

Safety reports are sent to the MB twice a year and will include a detailed analysis of study progress, data and safety issues.

3.2 Content of Data and Safety Monitoring Report

This section describes the content of the data and safety monitoring reports, including:

- *CONSORT diagram and actual versus expected enrollment figures that illustrate recruitment and participation status.*[1]
- *Data tables that summarize demographic and baseline clinical characteristics.*
- *Data quality tables that capture missing visits and missing case report forms.*
- *Safety assessments of aggregate tables of adverse events and serious adverse events.*
- *Listings of adverse events, serious adverse events, deaths, unanticipated problems and protocol deviations.*
- *Aggregate tables of clinical laboratory values.*

The specifics of the study and the requests of the monitoring entity will guide requirements for additional tables and listings. Tables for multi-site studies will present aggregated data as well as data by site.

Example: Demographic data will include sex, ethnicity, race, education and age and will be stratified by site.

Refer to the NIAMS Data and Safety Report Templates for guidance.

[1] Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. Ann Int Med 2010; 152.

3.3 Monitoring Body Membership and Affiliation

This section includes a roster of the monitoring entity's name(s) and affiliation(s).

Example: The following individual(s) has/have accepted position(s) as part of the Monitoring Body (MB). MB membership will be reviewed and approved by the NIAMS. Should there be any questions regarding the independence of the MB it will be addressed and corrected if necessary.

Name
Title, Organization

Name
Title, Organization

3.4 Conflict of Interest for Monitoring Bodies

This section describes the conflict of interest procedure for MB members.

Example: Monitoring body members should have no direct involvement with the study investigators or intervention. Each member will sign a Conflict of Interest Statement which includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or non-commercial interests pertinent to study objectives.

3.5 Protection of Confidentiality

This section describes how confidentiality of data presented to the monitoring entity will be protected.

Example: Only masked data will be presented during the open sessions of the MB. All data, whether in a report or discussed during a MB meeting are confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

3.6 Monitoring Entity Responsibilities

A charter provides a detailed list of the monitoring entity's responsibilities, which may include:

- *Reviewing the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, including all proposed revisions, and the Manual of Operating Procedures (MOOP), which may contain the sections included above.*
- *Evaluating the progress of the study on an ongoing basis including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of study site(s), and other factors that can affect the outcome.*

- *Evaluating proposed new sites (that differ from the approved application) and make a recommendation to the NIAMS as to whether the enrollment at the site(s) is expected to enhance overall enrollment. The evaluation of a proposed new site may include evaluating the patient population pool, catchment area description, recruitment plan and target enrollment for any new clinical sites.*
- *Considering the impact of factors external to the study when new information, such as scientific or therapeutic developments becomes available that may affect safety of participants, their willingness to participate in the study or the ethics and conduct of the study.*
- *Reviewing Unanticipated Problems, Serious Adverse Event reports and inform the NIAMS whether there is an effect on participant safety.*
- *Reporting any problems with study conduct or performance to the NIAMS.*
- *Ensuring the measures to ensure the confidentiality of study data and results are appropriate.*
- *Reviewing and evaluating requests for protocol modifications/amendments.*
- *Reviewing data after completion of each cohort to approve dose escalation, if applicable.*
- *Reviewing before study initiation the stopping rules and plans for interim analyses presented in the protocol. These plans outline the conditions under which a study may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures or other issues).*
- *Reviewing the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate or modify the study based on observed benefit or harm in accordance with the planned stopping rules.*